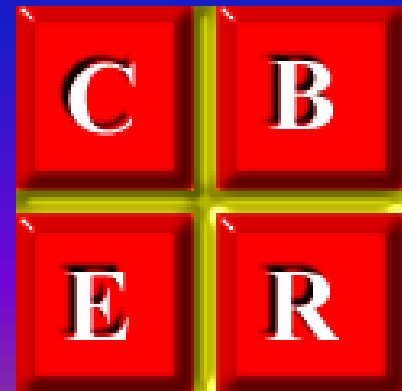
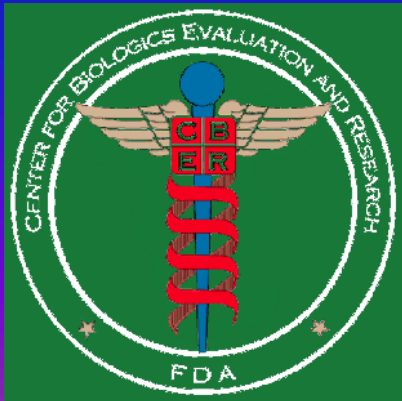


# Regulatory Issues in the Manufacture and Pre-clinical Testing of New Vaccines

Sheldon Morris, Ph.D.

Laboratory of Mycobacterial  
Diseases and Cellular  
Immunology

Center for Biologics  
Evaluation and Research



# **Current Good Manufacturing Practices**

# **Current Good Manufacturing Practices Regulations**

- **CGMP Regulations ( 21 CFR 210 and 211)**
- **General Biologic Product Standards (21 CFR 610)**
- **IND Regulations (21 CFR 312)**

# **Current Good Manufacturing Practices**

- Facilities**
- Equipment**
- Raw Materials and Components**
- Master Seed Production**
- Validated Procedures**
- Environmental Monitoring**
- Personnel**
- Batch Records**

# CGMPs - Facilities

- Adequate space
- Systems for monitoring environmental conditions
- Systems for monitoring equipment
- Air supplied through HEPA filters
  - Class 100 - 3,520 particles, 1 microbe/ m<sup>3</sup>
  - Class 100,000 – 3,520,000 particles, 100 microbes/ m<sup>3</sup>

# **CGMPs – Monitoring of the Environment and Water**

- **Evaluate the quality of air and surfaces**
  - **Surface, active air, and passive air monitoring**
- **Monitor water supplies**
  - **Microbial Contamination**
  - **Chemical Content**
  - **Water for Injection used for Product Components**
- **SOPs**
  - **Frequency and Time of Sampling**
  - **Duration of Sampling**

# CGMPs – Master Seed Lot Production and Characterization

- **Primary Seed Lot**
  - Important to produce sufficient primary seed
  - Store in 2 locations
  - Test for activity, contaminants, stability, etc.
  - Free from BSE
- **Secondary Seed Lot**
  - Generate secondary or working seeds from the primary seed
  - Characterize for activity, contaminants, etc.

# **CGMPs – Manufacturing Process Validation**

- **Entire Process standardized and validated (fermentation, harvesting, sterilization, cleaning, etc.)**
- **SOPs written for the entire Manufacturing Process**
- **Process standardization leads to Consistent Manufacturing**

# **CGMPs – Batch Production Record**

- **Complete Record of Entire Manufacturing Process**
- **Documents Every Step in the Manufacturing Process**
  - **Raw Materials (Potential BSE contamination)**
  - **Buffer and Media Production**
  - **Product Purification**
  - **Testing Results**
  - **Environmental Monitoring, etc.**

# **CGMP Summary**

- **Use Clean Air and Water**
- **Standardize and Validate the Manufacturing Process**
- **SOPs are Essential**
- **Document the Process**

# **Pre-Clinical Product Testing**

# Characterization of the Product

- **Safety** (21 CFR 600.3)
  - ✓ Relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered...
- **Purity** (21 CFR 600.3)
  - ✓ Relative freedom from extraneous matter in the finished product...
- **Potency** (21 CFR 600.3)
  - ✓ Specific capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

# Product Testing

- General Safety
- Sterility
- Potency
- Purity
- Identity
- Freedom from virulent mycobacteria
- Other relevant safety assays
- Stability

# General Safety

- Detection of extraneous toxic contaminants
- Required for biological products
- Method in 21 CFR 610.11
  - Injection into mice and guinea pigs
  - 7 day test period
  - Survival
  - Weight gain

# **Freedom from Virulent Mycobacteria**

- **Appropriate for live Mycobacterial Vaccine Strains or TB-derived Products**
- **Inject 6 guinea pigs with  $> 1$  Human dose**
- **Six week test period**
- **Examine post-mortem for evidence of tuberculous disease**

# Sterility

- Freedom from contaminating organisms
- 21 CFR 610.12 sterility test procedure
  - Fluid thioglycolate media
  - Soybean casein digest media
  - Strains to test for growth promotion of media
- Equivalent methods – USP methods
- Bioburden assessments required for live attenuated vaccine strains

# Potency

- Specific capacity to effect a given result
- Often shows that a biologic induces an appropriate immune response
- May not directly correlate with product efficacy
- In vivo or in vitro
- Measure of manufacturing consistency and stability

# Types of Vaccine Potency Assays

- **Mouse Protection Assay – Typhoid, Plague**
- **Guinea Pig Protection – Anthrax**
- **Toxin Neutralization – Tetanus, Diphtheria**
- **Viability – BCG**
- **DTH response – BCG**
- **ELISA to specific antigens – Acellular pertussis**
- **Saccharide/protein ratio – Pneumococcal, Haemophilus polysaccharide conjugates**

# Stability

- Defines product shelf-life (1 – 2 yrs)
- Stable product needed for clinical trials
- Establish program to evaluate stability at specific time intervals
  - Potency
  - Moisture
  - Sterility

# **Vaccine Manufacturing Submissions: Common Concerns**

- Insufficient information and documentation**
- Clinical lots not clearly identified**
- Inadequate product testing results**
- Inappropriate testing for adventitious agents or toxic components**

# **Vaccine Manufacturing Submissions: Common Concerns (cont.)**

- Inadequate stability testing**
- Inappropriate toxicology testing**
- Pre-clinical testing formulation differs from clinical vaccine formulation**

# CBER Guidance

- Web: [www.fda.gov/cber/reading.htm](http://www.fda.gov/cber/reading.htm)
- Email: [OCTMA@CBER.FDA.GOV](mailto:OCTMA@CBER.FDA.GOV)
- Fax: 1-888-CBER-FAX
- Phone
  - ✓ DVRPA: 301- 827-3070
  - ✓ OCTMA: 301- 827- 1800